Transfusion Medicine and Hemotherapy

Original Article

Transfus Med Hemother 2017;44:78–83
DOI: 10.1159/000464297

Received: January 2, 2017
Accepted: February 20, 2017
Published online: March 8, 2017

Thromboelastometry and Thrombelastography Analysis under Normal Physiological Conditions – Systematic Review

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Keywords
Thromboelastometry · Thrombelastography · Technical efficacy · Healthy subjects · Hemostasis

Summary
Background: Studies investigating thromboelastometry or thrombelastography analyses in a physiological context are scattered and not easy to access. **Objective:** To systematically retrieve and describe published reports studying healthy subjects and targeting at the correlation of ROTEM® and TEG® measurements with conventional parameters of hemostasis. **Methods:** Systematic Review: Papers were searched in Medline, Scopus and the Science Citation Index database. Reference lists of included studies and of reviews were screened. To be included papers had to report ROTEM or TEG data on healthy subjects. Two reviewers screened papers for inclusion, read full texts of potentially relevant papers, and extracted data of included papers. **Results:** Searches identified 1,721 records of which 1,713 were either excluded immediately or after reading the full text. The remaining 8 studies enrolled 632 subjects. The association of conventional parameters of hemostasis with ROTEM and with TEG was investigated in one and two studies, respectively. Overall correlation was limited and ranged from 0.0 to 0.40 (total thrombus generation vs. fibrinogen; clotting time INTEM vs. activated partial thromboplastin time). **Conclusions:** Studies assessing the relationship between thromboelastometry or thromboelastography analyses and conventional parameters of hemostasis in healthy subjects remains scarce, and correlations are limited. Further research is needed to understand the physiology of thromboelastometry and thromboelastography parameters.

Introduction

Back in 1978, Loop and Lusted [1] proposed the first phased evaluation of new medical tests. To date, after the publication of at least 18 additional recommendations, (reviewed in [2]) there is a broad consensus that first evaluations should address parameters of technical efficacy such as minimal detection level, circadian fluctuation, reproducibility, and correlation with established tests in healthy volunteers in order to understand the physiology of the analyzed parameters. It has been recognized that sophisticated and expensive tests that are disseminated without suitable evaluations can subsequently be found to have marginal clinical value and economic benefit. Well known examples include the carcinoembryonic antigen test in the diagnosis of colon cancer [3], iodine-125-labeled fibrinogen scans in the diagnosis of deep venous

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thrombi [4], or rapid magnetic resonance imaging in the management of patients with low back pain [5].

Thromboelastometry (ROTEM®) and thrombelastography (TEG®) analysis, two methods evaluating hemostasis, are increasingly used in clinical practice, based on the anticipation that they improve the management of acute bleeding [6, 7]. Several possible advantages over conventional laboratory parameters promote their use in emergency units and operating rooms. The analyzer is easy to use, and tests are readily available. Results are displayed graphically, allowing an intuitive interpretation [8]. Furthermore, tests claim to provide global information on all aspects of hemostasis, including fibrinogen level, platelet function, coagulation cascade, cross-linking of fibrin, and fibrinolysis. In addition, whereas the therapeutic consequences of results obtained with conventional parameters often remains uncertain, thromboelastometry/thromboelastography results suggest specific interventions to enhance hemostasis immediately [9]. Several studies explored their role in the detection of coagulopathies and changes in bleeding management as well as in the perioperative setting [10–14]. However, despite a vast amount of investigations, the clinical value of these methods has been challenged repeatedly [15–19]. It has been argued that the lack of rigorous examinations assessing the correlation of thromboelastometry and thromboelastography measurements with conventional parameters of hemostasis jeopardizes its clinical interpretation and usefulness [8, 20, 21].

To the best of our knowledge, however, there is no systematic review assessing the available evidence on thromboelastometry and thromboelastography examinations under physiological conditions in healthy volunteers. We therefore set out to systematically search, describe and inventory published reports on ROTEM and TEG data in healthy subjects, targeting at the correlation of thromboelastometry and thromboelastography measurements with conventional parameters of hemostasis.

Material and Methods

The present systematic reviews was done according to the PRISMA statement [22].

Search Strategy

To identify papers investigating correlations of ROTEM and TEG measurements with conventional parameters of hemostasis under physiological conditions, we searched (PRE-)MEDLINE (PubMed interface) using a search string including the two Medical Subject Headings (MeSH) 'Thrombelastography/methods'[Mesh], 'Blood Coagulation Tests'[Mesh] and the free text terms thromboelastography, thromboelastometry, ROTEM, and TEG. SCOPUS was searched using the following algorithm: TITLE-ABS-KEY(thromboelastography OR thromboelastometry)) AND (valid*) AND (LIMIT-TO(DOCTYPE, 'ar')) AND (LIMIT-TO(SUBJAREA, 'MEDI')). We also searched the Web of Science database entering 4 seminal papers [8, 23–25] and checked their citations for potentially relevant papers. Searches were complemented checking reference lists of included studies and of a recently published Cochrane review [15]. Electronic searches were done from inception to November 2016.

Selection Criteria for Inclusion

To be included a paper had to use whole blood or citrated blood obtained from healthy volunteers and had to assess either ROTEM or TEG. Additional criteria had to be fulfilled for inclusion of correlation studies: ROTEM and TEG data in combination with at least one established parameter of hemostasis such as activated partial thromboplastin time (aPTT), prothrombin time (PT), platelet count (PLT), fibrinogen level, or d-dimers.

Exclusion Criteria

We excluded papers assessing trauma patients, patients undergoing cardiac surgery, and other patients with severe illness as well as studies including pregnant women, children, or patients with sepsis if the study did not include any kind of control arm with healthy subjects.

Head-to-head comparisons between ROTEM and TEG were also excluded, if they were assessed in absence of an established hemostasis method.

Selection Process and Data Abstraction

In the case of multiple publications on the same participants, the most complete report was chosen for each study. We extracted data in duplicate, and a third reviewer resolved any discrepancies if the two reviewers disagreed. Of each study we extracted participants' age, number of female participants, the total number of included subjects, the device employed (ROTEM, TEG), and the hemostasis parameter assessed. In case of TEG studies these were reaction time (R time), time to maximum clot formation (K time), α angle, MA (maximal amplitude), SEMS (shear elastic modulus strength), CI (coagulation index), MTG (maximal thrombus generation), TMG (time to maximal thrombus generation), and TTG (total thrombus generation). In the ROTEM studies CT (clotting time), CFT (clot formation time), alpha angle, and MCF (maximum clot firmness) for both INTEM and EXTEM assay were recorded. Finally, we also extracted which of the established methods was used as the comparator test and what type of correlation or concordance parameters was used.

Thromboelastometry/Thromboelastography Analysis

The analytical principle of thromboelastometry and thromboelastography analysis is discussed in detail elsewhere [13, 20, 26–28]. In brief, the viscoelastic properties of a forming clot are assessed by recording the oscillations of a pin or a cup containing a citrated whole blood sample. Different aspects of clot formation are represented as parameters of the analysis. For example, the time from addition of the reagent until start of clot formation is denoted as CT in case of ROTEM, and R time in case of TEG; the clot strength is reported as MCF, or MA. Parameters are measured after addition of different activators. By analogy with PT, tissue factor reagent is added in case of EXTEM (ROTEM) and RapidTEG. Comparable to the aPTT, contact phase activators are added in case of INTEM (ROTEM) or standard TEG.

Results

Selection Process

Searches retrieved 1,721 records of which 1,588 had to be excluded after screening title or abstract. Full texts of 133 articles were examined for inclusion. Of these, 125 articles fulfilled at least one exclusion criterion leaving 8 articles for detailed examination [24, 29–35]. The selection process is described in figure 1.

Included Studies

Thromboelastometry or thromboelastography measurements in healthy volunteers have been performed in 8 studies, enrolling 632 subjects (table 1) [24, 29–35]. Five studies reported thromboelastometry/thromboelastography results but did not investigate correlations with conventional parameters of hemostasis [24, 29, 30, 34, 35]. Lang and colleagues [24] conducted a multicenter study to establish reference values for ROTEM thromboelastome-

Table 1. Characteristics of identified evaluation studies in healthy volunteers

Author, year	Mean age (SD), years	Age range, years	Female, n (%)	Total (n)	Device	Correlation/concordance
Lang et al., 2005 [24]	45.4 (17.6); 43.1 (15.9); 38.8 (14.4)	–	161 (61.5%)	262	ROTEM	–
Rivard et al., 2005 [32]	–	–	2 (50%)	4	TEG	linear/non-linear regression
Tripodi et al., 2009 [35]		20–60	28 (48%)	58	ROTEM	–
Huissoud et al., 2009 [30]	30 (median)	26–33	20 (100%)	20	ROTEM	–
Scarpelini et al., 2009 [34]	36.8 (11.2)	–	40 (34%)	118	TEG	–
Roeloffzen et al., 2010 [33]	49.5 (25.5)	19–87	60 (50%)	120	TEG	Pearson's correlation coefficients
Foley et al., 2012 [29]	–	29–32	0 (0%)	5	TEG	–
Kim et al., 2013 [31]	44	22–71	19 (42%)	45	ROTEM	Pearson's correlation / linear regression

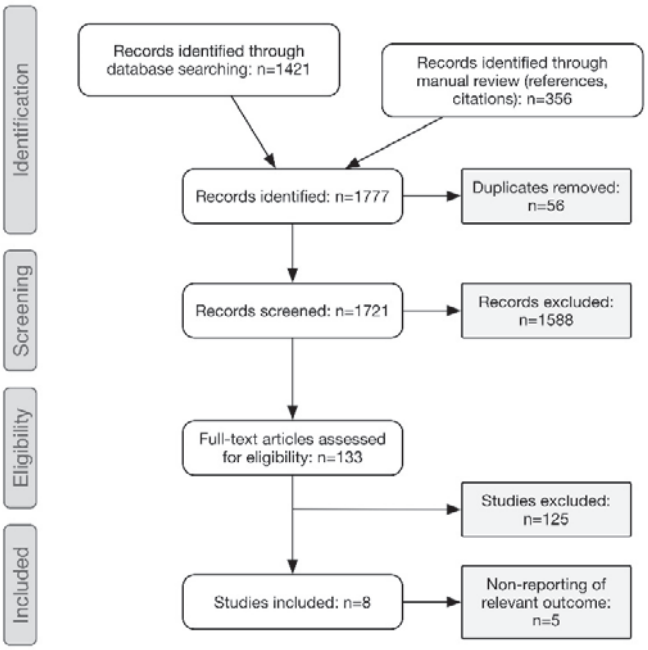

Fig. 1. Study flow.

try. 262 individuals were included in five centers in Germany, Austria, and France. Even though considerable variation between centers existed, 'orientating reference ranges' were calculated for INTEM, EXTEM, and FIBTEM parameters (CT, CFT, α angle, A10, A20, A30, MCF, CLI30, and ML). Tripodi and co-workers [35] conducted ROTEM measurements in 58 healthy volunteers to establish reference ranges for an observation study in cirrhosis patients. However, results were not reported, and no correlation studies have been done. 20 healthy women were studied using ROTEM in an investigation by Huissoud and colleagues [30], serving as a control for thromboelastometry patterns in pregnancy. Median values and inter-quartile ranges of EXTEM, INTEM, FIBTEM, and APTEM parameters were reported. TEG was conducted in 5 volunteers in a study by Foley et al. [29] aiming to improve the thromboelastography assay, and individual measurements were reported.

Correlation with Conventional Parameters of Hemostasis

Three studies reported the extent of association between thromboelastometry/thromboelastography parameters and conventional coagulation assays [31–33]. The details are reported in table 2. Two studies focused on thromboelastography [32, 33]. In a study enrolling 120 participants (50% female) of 49.5 years on average, Roeloffzen and colleagues [33] compared R time with the aPTT, K time with the hemoglobin level, aPTT and the fibrinogen level, α angle with aPTT and the fibrinogen level, MA with the fibrinogen level, SEMS with the fibrinogen level, the CI with aPTT and the fibrinogen level, MTG with the fibrinogen level, TMG with aPTT, and the TTG with the fibrinogen level. Pearson's correlation coefficient was reported and varied between 0.21 (TMG vs. aPTT) and 0.40 (TTG vs. fibrinogen level). Rivard and co-workers [32] studied the association between a TEG parameter used as surrogate for TTG with thrombin generation as measured using thrombin/antithrombin complexes (TAT) in 4 volunteers. A correlation coefficient of 0.85 was determined from a linear regression and a correlation coefficient of 0.94 from a linear regression using the ln of TAT.

Associations between thromboelastometry parameters and conventional parameters of hemostasis were investigated in one study only [31]. Kim and co-workers [31] correlated CT, CFT, α angle, CFR, and MCF with PT as well as aPTT. No significant correlation was found between any EXTEM or INTEM parameters and PT. For INTEM, the CT value was significantly correlated with aPTT only ($r = 0.41$).

Discussion

Main Findings

Using comprehensive retrieval methods, our systematic review only found few studies assessing thromboelastometry as well as thromboelastography and correlations thereof with established parameters of hemostasis in healthy volunteers. The studies revealed only a weak correlation.

Findings in Context

There are several studies investigating the relationship of thromboelastometry or thromboelastography in animals, e.g.,

Table 2. Correlation of thromboelastometry/thromboelastography parameters with conventional parameters of hemostasis in healthy volunteers

Author, year	n	Device	Test	Pearson's correlation coefficient				
				Hb	[a]PTT	PT	fibrinogen	TAT
Roeloffzen et al., 2010 [33]	120	TEG	R time	NS	0.36 ($p < 0.05$)		NS	–
	120	TEG	K time	0.24 ($p < 0.05$)	0.24 ($p < 0.05$)		–0.27 ($p < 0.05$)	–
	120	TEG	α angle	NS	–0.22 ($p < 0.05$)		0.28 ($p < 0.05$)	–
	120	TEG	MA	NS	NS		0.37 ($p < 0.05$)	–
	120	TEG	SEMS	NS	NS		0.37 ($p < 0.05$)	–
	120	TEG	CI	NS	–0.21 ($p < 0.05$)		0.25 ($p < 0.05$)	–
	120	TEG	MTG	NS	NS		0.27 ($p < 0.05$)	–
	120	TEG	TMG	NS	0.21 ($p < 0.05$)		NS	–
	120	TEG	TTG	NS	NS		0.40 ($p < 0.05$)	–
Rivard etal., 2005 [32]	4	TEG	TTG	–	–		–	0.85[#] / 0.94[†] ($p < 0.05$)
Kim et al., 2013 [31]	45	ROTEM	CT EXTEM	–	–0.223 ($p = 0.17$)	–0.137 ($p = 0.46$)	–	–
	45	ROTEM	CFT EXTEM	–	–0.149 ($p = 0.36$)	–0.189 ($p = 0.24$)	–	–
	45	ROTEM	α angle EXTEM	–	0.079 ($p = 0.63$)	0.005 ($p = 0.89$)	–	–
	45	ROTEM	MCF EXTEM	–	0.005 ($p = 0.97$)	–0.164 ($p = 0.31$)	–	–
	45	ROTEM	CT INTEM	–	0.406 ($p = 0.009$)	0.12 ($p = 0.46$)	–	–
	45	ROTEM	CFT INTEM	–	–0.12 ($p = 0.46$)	–0.194 ($p = 0.23$)	–	–
	45	ROTEM	α angle INTEM	–	–0.053 ($p = 0.75$)	0.122 ($p = 0.45$)	–	–
	45	ROTEM	MCF INTEM	–	–0.014 ($p = 0.93$)	0.003 ($p = 0.98$)	–	–

[a]PTT = Activated partial thromboplastin time; CI =coagulation index; CT = clotting time; CFT = clot formation time; Hb = hemoglobin level; K time = time to maximum clot formation; MA = maximal amplitude; MCF = maximum clot firmness; MTG = maximal thrombus generation; NS = not stated; PT = prothrombin time; R time = reaction time; SEMS = shear elastic modulus strength; TAT thrombin/antithrombin complex; TMG = time to maximal thrombus generation; TTG = total thrombus generation.
[#]Derived from linear regression analyses.
[†]Derived from log-linear regression analysis (ln(TAT)).

Mauch et al. [36]. In this study the intrarater and interrater validity of the ROTEM data was analyzed with blood from healthy pigs. Another prospective study compared the coagulation profiles of healthy foals using standard techniques (PT, aPTT, fibrinogen concentration, and antithrombin) with the TEG analyzer [37]. The validity of the ROTEM and TEG was verified through comparison with standard methods in the context of specific circumstances, as for example orthotropic liver transplantation [38–40], during aortic surgery [12, 41, 42], or in trauma patients [18, 43, 44]. We also found a few trials reporting on head-to-head comparisons between ROTEM and TEG [21, 45, 46]. Although these approaches also yield valuable information, we think that they do not make comparisons with standardized methods in healthy subjects superfluous.

Strength and Limitations

We applied up-to-date and rigorous systematic review methods to retrieve and assess the available evidence. In view of the risk that potentially relevant studies could be missed due to ambiguous indexing in the various databases, we applied an over-inclusive approach. These sensitive searches retrieved over 1,700 records. Screening for inclusion was made in duplicate to reduce the risk to miss relevant papers. We expected to find a reasonable number of studies that would allow us to provide quantitative summaries of various comparisons. Moreover, out of the many available, we hoped to depict those parameters from thromboelastometry and thrombelastography that would be most suited for investigations in various clinical settings such as acute bleeding, applications in emergency rooms, and for treatment of patients with specific hemostatic deficiencies. Despite our motivation, the current evidence base impeded us from generating meaningful summaries for further research and clinical practice.

Implications for Clinical Practice

The small number of studies examining thromboelastometry or thromboelastrography in a cohort of healthy volunteers and systematically comparing the so obtained findings to conventional assays of hemostasis is remarkable. One may argue that the clinical value of established coagulation parameters is limited as well. It is true that results of coagulation parameters such as PT not directly prompt any specific treatment. Nevertheless, they are still important biomarkers for the detection of coagulopathies in the setting of acute bleeding [47–49].

Implications for Research

Following existing guidelines of test evaluation (reviewed and discussed in [2]), we propose that further research should first investigate the distribution of normal values of ROTEM and TEG parameters in reasonably sized studies enrolling healthy subjects. Second, distributions should be assessed in groups of patients with a specific illness and compared to distributions of healthy subjects. In a third step, assessing test performance characteristics such as sensitivity and specificity should be performed, taking contextual clinical information into account. Fourth, studies should determine the added value of thromboelastometry/thromboelastography in context of other clinical information about the patients' state that is available prior testing. Finally, decision-analytic models should be performed determining the optimal areas for clinical use, taking clinical outcomes into account.

Conclusions

Studies assessing the relationship between thromboelastometry or thromboelastography analyses and parameters of hemostasis in healthy subjects remains scarce. From a hemostaseologic standpoint, further physiologic research is needed to elucidate the significance of thromboelastometry and thrombelastography for clinical practice and research.

Disclosure Statement

Financial support for the submitted work was received from the Research Fund Haematology Cantonal Hospital Lucerne. The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. MN has received research grants, lecture fees, or consultancy fees from Bayer, Roche Diagnostics, Instrumentation Laboratory, Boehringer Ingelheim, and CSL Behring.

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